Remarks

1. General Matters

The action mistakenly refers to claims 84 and 85 as withdrawn from consideration. As it correctly noted, the last numbered pending claim was 83.

Also, the office action summary identifies claims 13 and 14 as withdrawn, whereas it is clear from page 2, second to last paragraph that claims 14 and 15 were intended; claim 13 is drawn to the elected species.

2. Claim Amendments

Claim 1 has been amended as follows:

> A vaccine composition comprising ~~an isolated protein belonging to the Bcl-2 protein family or~~ an immunogenically active peptide ~~fragment hereof~~ or a nucleic acid encoding ~~said protein or~~ said peptide ~~fragment for use as a medicament~~, wherein the peptide consists of at the most 15 amino acids and comprises SEQ ID NO:8 or a sequence which differs from SEQ ID NO:8 by one or two amino acid substitutions.

Basis for this amendment can be found in the application as filed on p. 15, l. 34 to page 16, l. 11 (for the length limitation) and on page 14, l. 18 to 22 (for the amino acid substitution limitation).

Parallel amendments have been made to claim 10, drawn to the peptide per se rather than to the vaccine composition.

Since claims 1 and 10 no longer use the term "fragment", conforming amendments have been made to the dependent claims. However, the use of "fragment" in claims 44-47 is still proper.

We have amended claim 7 (dep on 1) and 13 (dep on 10) to

recite that the peptide is a fragment of Bcl2, and claim 23 to require that the peptide comprises SEQ ID No: 8. Claim 33 has been amended to require that the peptide is a decapeptide, as, given the amendment of the base claim, it can no longer be a nonapeptide.

New claim 84 requires that the peptide consists of SEQ ID NO: 8.

New claim 85 recites that the peptide is capable of eliciting a BCl2-specific T-cell response, cp. original claim 3; basis for T-cell response is at e.g. P5, L25-26.

New claim 86 combines the limitations of claims 13 and 23.

New claim 87 requires that the peptide comprise a sequence which differs from SID 8 by at most one substitution, basis at P14, L18-22.

New claim 88 requires that any substitution of amino acids in the sequence corresponding to SID 8 not affect the residues corresponding to the HLA-A2 anchor positions as set forth on page 14, i.e., positions 2, 6 and 10 (the C-terminal of SID 8).

New claim 89 requires that the sequence satisfy the stated HLA-A2 motif for the positions corresponding to positions 2 and 10 of SID 8. Note that SID 8 has S, not V, at position 6.

Hence, new claim 90 is drawn to the peptide comprising the variant of SID 8 wherein position 6 is V (consistent with the HLA-A2 motif as stated on page 14).

New claims 91-93 parallel 88-90 except they are dependent on 87.

Claims 4-6, 11, 12, 14, 15, 31, 32, 34-36,and 82 have been cancelled in view of the amendment of claims 1 and 10.

Claims 8, 9, 24-28 have been cancelled as drawn to an unelected species, and 67-70 and 83 as drawn to an unelected group.

Rejoinder of the method claims dependent on claims 1 and 10

is respectfully requested, as claims 1 and 10 are now believed to be allowable. See MPEP 821.04.

3. Novelty Issues

3.1. The Examiner finds that the present invention lacks novelty over Akatsuka et al. The document describes peptides derived from Bcl-2A1. The peptides have been identified as epitopes recognised by HLA restricted CTL clones isolated from cancer patients having received bone marrow transplantation.

The Bcl-2A1 gene is a minor histocompatibility antigen which is only expressed in haematopoietic cells. Minor histocompatibility antigens are receptors on the cell surface that are known to give an immunological response. The Bcl-2A1 gene is thus different from the Bcl-2 gene described in the present invention, which is specifically described to be capable of binding to MHC (Major Histocompatibility) Class I HLA molecules and thereby eliciting CTL immune responses in patients suffering cancer disease (section [0017])

In particular, Akatsuka et al. does not disclose the the specifically claimed peptide (SEQ ID NO 8), nor a peptide of at the most 15 amino acids comprising SEQ ID 8. Nor does Akatsuka disclose a peptide of at most 15 amino acids that comprises SEQ ID NO:8 or a sequence that difffers from SEQ ID NO:8 by at most two amino acid substitutions.

Accordingly, Akasuka also does not describe a vaccine composition comprising such peptides. In fact, Akatsuka et al. suggests the use of Bcl-2A1 specific T-cells in immunotherapy and hence does not describe any vaccine composition comprising immunologically active Bcl-2A1 peptide.

We respectfully hold the opinion that the present invention is novel over Akatsuka et al.

3.2. The Examiner further states that the present invention lacks novelty over Saeterdal et al. This document describes various cancer-related genes including BAX and discloses several BAX peptides. The T-cell responses to the BAX peptides are evaluated , however, no evidence was found for T-cells specific for the mutant Bax peptides in the examined patients (page 13260, 2. coloumn).

None of the described Bax peptides has significant sequence homology with SEQ ID NO 8, and nowhere in the document is a vaccine composition comprising an immunologically active Bcl-2 protein or peptide (more specifically SEQ ID NO 8) capable of binding to the MHC molecule HLA-A2 described. Hence, we respectfully hold the opinion that the present invention is novel over Saeterdal et al.

3.3. Finally, the Examiner finds that the present patent application lacks novelty over US 5,789,201 which describes the mammalian gene coding for Bcl-y. The sequence homology of Bcl-y and Bcl-2 is disclosed and there is said to be 43% sequence identity between the two. A **21** amino acids long fragment of Bcl-y is described with comprises a sequence of amino acids with 100% sequence identity with SEQ ID NO 8; however, the document does nowhere describe an immunogenically active peptide fragment consisting of at the most 15 amino acids and comprising SEQ ID NO:8 or a homologue thereof wherein 1 to 2 amino acids has been exchanged for another amino acid. Furthermore, the use of the particular peptide (SEQ ID NO: 13) is not described or speculated on. No use or function of this Bcl-y fragment is hence described and the particular fragment is not in any way described as particularly interesting or useful in vaccine compositions for cancer therapy. Since the present invention relates to a vaccine composition comprising SEQ ID NO 8, we respectfully hold the opinion that the present invention is novel over US 5,789,201.

4. Obviousness Issues

The Examiner finds that the present invention is obvious over Saeterdal et al. combined with Akatsuka et al.

Saeterdal et al. teaches that BAX is a cancer related gene and that several peptides derived from BAX potentially may be used to stimulate T-cells from patients.

Akatuska et al. teaches that T-cell epitopes from Bcl-2 family protein (Bcl-2A1) shows strong T-cell responses and speculates that these peptides could potentially be used for immunotherapy.

Both of the disclosed documents have as an objective to achieve T-cell specific responses to proteins and peptides. Saeterdal et al. however fails to demonstrate that Bax derived peptides elicits a T-cell specific response in the patients examined. In contrast, no specific T-cell response was detected. On p. 13260, 2nd col. The authors states that "In the experiments reported here, we did not find evidence for T cells specific for mutant Bax peptides in the patients." Hence, Saeterdal et al. gives no indication of any beneficial effect of the disclosed Bax derived peptides.

Akatsuka et al. describes how T-cells specific for Bcl-2A1, a minor histocompatibility antigen which is only expressed in haematopoietic cells, can be used in immunotherapy.

Neither Saeterdal et al. nor Akatsuka et al. discloses a vaccine composition comprising immunologically active Bcl-2 peptides (e.g. SEQ ID NO 8) capable of binding to the MHC molecule HLA-A2, and neither of the documents contemplates on the idea of such a vaccine composition.

In contrast the present application describes specific T-cell responses in a number of cancer patient to peptides comprising SEQ ID NO: 8 (see Examples 1 and 2).

We therefore respectfully suggest that the present invention would not have been obvious over the prior art.

Respectfully submitted,

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